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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,530	11/28/2000	Clay B. Siegall	9632-012	7001

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	11

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,530	SIEGALL ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *26,27,32,33 and 37-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *26,27,32,33, 37-66, 68, 75-80, 82-114* is/are rejected.

7)☐ Claim(s) *67, 69-74, 81* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *11* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

2. Claims 26, 27, 32, 33 and 37-114 are pending and under consideration.

3. After review and reconsideration, the Office action of Paper No. 10 is vacated.

4. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 22, 2002 has been entered.

5. Claims 26, 27 and 37 have been amended. Claims 58-114 have been added. Claims 26, 27, 32, 33 and 37-114 are pending and under consideration.

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 31, lines 12 and 33; page 32, line 5 and page 46, lines 1 and 3. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

7. Claims 67, 69-74 and 81 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot serve as a basis for other multiple dependent claims. See MPEP § 608.01(n). Accordingly, claims 67, 69-74 and 81 have not been further treated on the merits.

8. Claims 60, 61, 62, 68, 75-80, and 82, 86-89, 95, 98, 101, 104, 107, 110 and 113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims

60 and 61 are rendered vague and indefinite by reference to a trade name, the object of which can be variable.

9. Claims 27, 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Claims 32, 33, 39, 42, 52-57, 87-89, 95, 98, 101, 104 and 107 are rejected in part as they depend on claim 27. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Applicant's referral to the deposit of the hybridoma secreting the S2C6 antibody on page 58 of the specification is insufficient assurance that all the conditions of 37 CFR 1.801-1.809 have been met.

It is noted that the deposit was made under the provisions of the Budapest Treaty, therefore, the filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

10. Claims 26, 27, 32, 33 and 37-114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating cancer, does not reasonably provide enablement for methods of preventing cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The instant claims are drawn in part to methods of preventing cancer in a subject. This would require administration of

the disclosed antibodies and molecules prior to the development of the cancers. However, there is no guidance in the specification for determining the appropriate time prior to the development of tumors to begin the therapy or for identifying patients who will develop cancers treatable by the claimed methods. Neither any art of record, nor the specification provides guidance with regard to the issues raised above. In view of the state of the art with regard to the prediction of cancer occurrence and the lack of teachings in the specification regarding how to select patients who will develop cancers treatable by the claimed methods and when to begin the claimed methods on said patients, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

11. Claims 26, 44-46, 49, 61, 62, 75 and 78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human antibodies which can compete for binding with S2C6, does not reasonably provide enablement for human antibodies which comprise SEQ ID NO:2-4 and 7-10, or human antibodies comprising sequences having at least 80% amino acid identity to SEQ ID NO: 8-10 or a human antibody comprising at least two CDR sequence selected from the group consisting of SEQ ID NO:8-10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claims 49 and 78 embody methods of claims 26 and 61 wherein said antibody is a human antibody. The art teaches the screening of human immunoglobulin libraries for antibodies that bind specific antigens (see rejection below). The art does not teach the selection of antibodies which bind to a specific antigen, wherein said antibodies would have a specific amino acid sequence in the variable chains or CDR. It is noted that the antibodies are screened for binding specificities not for amino acid sequence. There are no teaching in the art or the specification on how to make a human antibody comprising the instant CDR or variable chain regions and it is unclear if the human immunoglobulin repertoire would even have the claimed amino acid sequences as the murine S2C6. The specification provides no teachings addressing these concerns and no teachings specifically drawn to how to make a human antibody comprising the required amino acid sequences. It flows logically from this, that if one of skill in the art cannot make the antibodies upon which the instant method claims depend , one cannot use the claimed methods.

Given the state of the art and the lack of teachings in the specification, one of skill in the art would be subject to undue experimentation in order to make the claimed human antibodies and therefore use the claimed methods.

12. Claims 37, 40, 41, 42, 44-51, 63, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)As drawn to molecules without structural characterization

Claim 37 is drawn to a method for the treatment of cancer comprising the administration of a molecule which immunospecifically binds CD40, which molecule increases the binding of CD40 ligand to cell surface CD40 by at least 45% in addition to CD40 ligand. Claims 40 embodies the method of claim 37 wherein the molecule is conjugated to a chemotherapeutic agent. Claims 41, 42 and 44-51 are dependent in part on claim 37. Claim 63 is drawn to a method for the treatment of cancer comprising administering to a subject a molecule that binds to CD40 and increases the binding of CD40 ligand to CD40 on B cells by at least 45% and comprises a human immunoglobulin constant domain. Claims 37 and 40 are method claims which are dependent upon a genus of molecules which bind to CD40 and increase the binding of CD40 ligand to CD40 receptor by at least 45%. When given the broadest reasonable interpretation the claims encompass molecules which are not proteins or antibodies, and which bind to an epitope of CD40 which is not the epitope to which the S2C6 antibody binds. The genus of encompasses molecules which do not comprising antigen-binding portions of the S2C6 antibody and which do not bind to CD40 at the same epitope as the S2C6 antibody. Thus the genus of molecules is highly variant encompassing structures which have unlimited structural alterations from the disclosed S2C6, and which have functional attributes which differ from the S2C6 antibody, such as binding to an CD40 epitope which differs from the S2C6 epitope. The disclosure of the S2C6 antibody does not adequately describe this genus of molecules because the structural and functional attributes of the genus vary from the structural and functional attributes of the S2C6 antibody. One of skill in the art would reasonably conclude that applicant

was not in possession of the genus of antibodies on which the claimed method depends, therefore the methods lack adequate written description.

(B)As drawn to protein variants of SEQ ID NO:7 and protein variants of SEQ ID NO:8, 9 and 10.

Claim 60 is drawn to a method of treating cancer comprising the administration of a protein comprising an amino acid sequence that comprises regions having at least 95% identity to SEQ ID NO:7, wherein said protein binds CD40 and has an immunoglobulin constant domain. Claim 61 is drawn to a method of treating cancer comprising the administration of a protein comprising an amino acid sequence that comprises regions having at least 80% identity to SEQ ID NO: 8, 9 and 10, wherein said protein binds CD40 and has a human immunoglobulin constant domain. Claim 62 is drawn to the method of claim 61 wherein the protein comprises at least two of SEQ ID NO:8, 9 or 10. When given the broadest reasonable interpretation, the claimed methods rely upon a genus of proteins which vary from the structure of S2C6 and which encompass different functional attributes of S2C6 because the claims are not limited to those antibodies which bind to the same epitope of CD40 as S2C6. Thus the claims rely upon a genus of proteins which are structurally and functionally variant. The disclosure of the S2C6 antibody does not adequately describe this genus because the genus permits members having different structural and functional attributes from the S2C6 antibody. One of skill in the art would reasonably conclude that applicant was not in possession of the genus of antibodies on which the claimed method depends, therefore the methods lack adequate written description.

13. Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77 and 83-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melief et al (U.S. Application 2003/0022860, priority to May 23, 1998, cited in a previous Office action) in view of deBoer (U.S. 5,874,082, cited in a previous Office action).

Claim 26 is drawn to a method of treating cancer in a subject comprising administering to said subject an amount of a molecule comprising SEQ ID NO:2, 3, 4, 7, 8, 9, or 10, which molecule binds CD40, increases the binding of CD40 ligand to CD40 on B cells by at least 45% and comprises a human immunoglobulin constant domain. Claim 27 is drawn to a method of treating cancer comprising administering to the subject an amount of purified protein which

protein competes for binding to CD40 with monoclonal antibody S2C6 as secreted by the hybridoma of ATCC Accession Number PTA-110, increases binding of CD40 ligand to CD40 on B cells by at least 45% and comprises a human constant domain. Claim 59 is drawn to a method for treating cancer in a subject comprising administering to the subject a molecule comprising SEQ ID NO:8, 9 and 10, which molecule binds CD40 and comprises a human immunoglobulin constant domain. Claim 60 is drawn to a method of treating cancer in a subject comprising administering to the subject an amount of a protein comprising an amino acid sequence that has at least 95% identity to SEQ ID NO:7, which protein binds CD40 and comprises a human immunoglobulin constant domain. Claim 61 is drawn to a method for treating cancer comprising administering to a subject an amount of protein comprising an amino acid sequence that comprises regions having at least 80% identity to SEQ ID NO:8, 9 and 10 which protein binds CD40 comprises a human immunoglobulin constant domain. Claim 63 is drawn to a method of treating cancer comprising the administration of a molecule that binds to CD40 and increases the binding of a CD40 ligand to cell surface CD40 on a B cell by at least 45%, and comprises a human immunoglobulin constant region. Claim 64 is drawn to a method for the treatment of cancer comprising the administration of a molecule which competes with S2C6 for binding to CD40 , wherein said molecule comprises at least 2 CDR sequences selected from the group consisting of SEQ ID NO:8, 9 and 10 and comprises a human immunoglobulin constant domain.

The specification teaches on page 5, lines 10-14 that said chimeric or humanized antibodies are constructed based on the variable chain and CDR regions of the S2C6 antibody and that SEQ ID NO:2 and 7 are the variable chains of said antibody and SEQ ID NO:3, 4, 8, 9 and 10 are the CDR of the S2C6 antibody. When given the broadest reasonable interpretation the claims encompass the administration of a chimeric or humanized version of the S2C6 antibody.

Melief et al teach a method of treating cancer comprising the administration of CD40 binding molecules (abstract, claims 5-9, 11-13). Melief et al teach that the "triggering" of the CD40 in vivo can replace the requirement of a T-cell helper signal (examples 1 and 2 [0045]) and concludes that CD40 activation in the presence of tumor derived peptide reverses peripheral tolerance and results in tumor specific immunity (lines 22-24 of [0045]). Melief et al teach that

the CD40 binding molecules include antibodies [0008] and that humanized antibodies are preferred for the treatment of human subjects [0030]. Melief et al teach that the administration of CD40-binding molecules enhances the efficacy of anti-cancer vaccines comprising tumor specific peptides [0047]. Melief et al teach FGK45 as a CD40 activating antibody (line 5 of [0020]). Melief et al do not teach that administration of a humanized S2C6 antibody for the treatment of cancer.

deBoar teaches that anti-CD40 antibodies known in the art [prior to the disclosure of deBoar] have a stimulatory effect on human B cells (column 2, lines 45-46 and 62-64). deBoar teaches that the prior art anti-CD40 antibodies mimic the effect of T-helper cells and thus can replace the T cell helper signal (column 2, lines 51-59). deBoar teaches "new" antibodies such as 5D12, 3C6 and 3A8 which differ from the prior art anti-CD40 antibodies in that the new antibodies inhibit the B-cell stimulatory response (column 2, lines 62-67). deBoar teaches S2C6 as an "old" antibody (in contrast to the "new" antibodies) which stimulates B-cell proliferation (column 17, lines 57-62, and the description for Figures 5 and 6). deBoar teaches that the "new" antibodies can inhibit stimulatory signals elicited by the "triggering" of CD40 with another antibody (column 18, lines 36-40). One of skill in the art would reasonably conclude that the "old" S2C6 antibody "triggers" CD40. deBoar teaches that the administration of humanized versions of the "new" antibodies would be efficacious in the treatment of antibody-mediated autoimmune diseases (column 3, lines 52-65 and column 4, lines 14-19).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat cancer in a subject comprising the administration of a humanized or chimeric version of S2C6. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Melief et al regarding: the administration of FGK45 as a CD40 activating antibody in a method of treating cancer, and the general teachings of Melief et al on the importance of anti-CD40 antibodies in combination with tumor specific peptides for the reversal of immunological tolerance to said tumor specific peptides; in addition to the teachings of Melief et al on the importance of "triggering" CD40 in vivo for the induction of tumor specific immunity; and the teachings of deBoar on the triggering of CD40 by the "old" S2C6 antibody. One of skill in the art would specifically select the S2C6 antibody as an antibody which would trigger CD40 in vivo and

replace the required T-cell helper signal needed to induce immunity rather than tolerance to a specific antigen.

Claims 26, 27, 63, 86-93 specify that the binding of the molecule increase the binding of the CD40 ligand by 45%, and up to at least 65%. It is noted that none of the references teach that the binding of the S2C6 antibody or the humanized version thereof results in the increase in CD40 ligand binding to the CD40 receptor by at least 45%. It is noted that Bjorck et al (Immunology, 1994, Vol. 83, pp. 430-437, cited in a previous Office action) teach that soluble CD40 ligand and the S2C6 antibody synergize in inducing proliferation of B-cells (page 433, , column 1, bridging sentence, and Table 2 "Il-4 + S2C6 + gp39") which is consistent with increasing the binding of the ligand. Furthermore, this would be an inherent property of the claimed antibodies derived from S2C6 because the S2C6 antibody and the humanized or chimerized S2C6 antibody taught by the specification would bind toCD40 at the same epitope, and thus, the interaction of the CD40 ligand with CD40 would be effected by the same alteration in structure resulting from the binding of an antibody to the S2C6 epitope. Thus, it would be inherent that the humanized or chimeric antibody derived from S2C6 would increase the binding of CD40 ligand to CD40, because the process of humanization would not alter the epitope to which the humanized antibody binds and thus the impact of the binding of the humanized or chimerized antibody on the CD40 molecule would be determined by the binding of the antibody to the S2C6 epitope. Applicant has previously argues against the teachings of Bjorck et al stating that they taught away from the instant invention because of the results of the ELISA assay presented in Table 4, wherein it is indicated that S2C6 inhibits the binding of gp39 by 57.9%. This has been considered but not found persuasive. Table 2 of Bjorck et al teaches the synergism of gp39 and S2C6 in the proliferation of B cells: entries five and six indicate the uptake of tritiated thymidine in B-cells resulting from contact with S2C6 at two different concentration, entries 9 and 10 indicate the uptake of tritiated thymidine in B-cells resulting from contact with gp39 at two different concentrations, entries 19 and 20 indicate the uptake of tritiated thymidine resulting from contact with both S2C6 and gp39. It is clear from this data that the resulting proliferation induced by the combination of S2C6 and gp39 is far in excess from that expected from an additive effect of S2C6 and gp39. Further, the results in Table 4 which indicate that S2C6 inhibits the biding of gp39 in the ELISA assay are not germane to the instant case. The

results set forth in Table 2 are for the binding of S2C6 to CD40 on the cell surface, the results indicated for table 4 represent the binding of S2C6 and gp39 to the CD40-Ig fusion protein which was immobilized on the surface of the 96-well plate (page 431, second column, lines 3-12, under the heading "Epitope analysis"). Given that the results of the activation of cellular proliferation presented in Table 2 showed synergistic effects with the addition of S2C6 and gp39, one of skill in the art would reasonably conclude that ELISA data on the competition with binding to a CD40-Ig coated solid support does not accurately mimic CD40 receptor on a cell surface.

14. Claims 26, 27, 33, 41, 42, 44-48, 50, 52-56. 57, 59-65, 68, 75-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melief et al (U.S. Application 2003/0022860, priority to May 23,.1998) and de Boer (U.S. 5,874,082) as applied to claims 26, 27, 33, 41, 42, 44-48, 50, 52-55. 57, 59-65, 68, 75-77 and 83-93 above, and further in view of Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, pp. 3-4, cited in a previous Office action). Claims 49, 56 and 78 specify that the antibodies which bind to CD40 are human antibodies.

The combination of Melief et al (U.S. Application 2003/0022860, priority to May 23, 1998) and de Boer (U.S. 5,874,082) render obvious claims 26, 27, 33 and 37, 41-48, 50-55. 57-65, 68, 75-77 and 82-114 with regard to a humanized S2C6 antibody or a single chain fragment thereof. The aforesaid references do not teach a human antibody which binds to CD40.

Clark teaches that the generation of human antibodies form combinatorial libraries of human immunoglobulin repertories as an alternative strategy to the humanization of rodent antibodies in the avoidance of the anti-globulin response associated with the administration of rodent antibodies to humans ((1)The anti-globulin response, page 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to screen a combinatorial library of human immunoglobulin genes to identify a human antibody which binds to the S2C6 epitope of CD40 and use said human antibody in the method of treating cancer as rendered obvious by the combination of Melief et al and deBoar. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the Clark on the generation of human

antibodies as a means for overcoming the anti-globulin response. It would be expected that a human antibody which binds the same epitope as the murine S2C6 antibody would cause the triggering of CD40 receptor resulting in proliferation of the B-cell in the same manner as the S2C6 antibody, because the binding to the S2C6 epitope on CD40 would induce the same intracellular signaling in the B-cell.

15. Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 83-96 and 100-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Funakoshi et al (Blood, 1994, Vol. 83, pp. 2787-2794) in view of Bjorck et al (Immunology, 1994, Vol. 83, pp. 430-437) and deBoar (U.S. 5,874,082) as evidenced by Unkun et al (Blood, 1990, Vol. 76, pp. 2449-2456).

Claim 32 embodies the method of claims 26 or 27 wherein CD40 ligand is administered. Claim 43 embodies the method of claim 26 wherein CD40 ligand is administered. Claim 37 is drawn to a method for the treatment of cancer comprising administering CD40 ligand in addition to a molecule that immunospecifically binds to CD40, wherein said binding increases the binding of the CD40 ligand by 45% . Claims 51 and 57 embody the methods of claims 50 and 52, respectively, wherein said methods further comprise the administration of CD40 ligand. Claim 82 embodies the method of claims 61 or 62 further comprising administering CD40 ligand. Claims 94-96 embody the methods of claims 26, 27, 59, 63, 64, 87, 91, wherein the cancer is a hematological malignancy. Claims 100-102 embody the methods of claims 94-96 wherein the hematological malignancy is chronic leukemia, lymphoma or multiple myeloma. Claims 103-105 embody the methods of claims 100-102 wherein the leukemia is chronic lymphocytic leukemia. Claims 106-108 embody the methods of claims 100-102 wherein the lymphoma is non-Hodgkin's lymphoma.

Funakoshi et al teach that B-and T-cell malignancies can be arrested by exposure to stimuli that lead to activation in normal B or T cells. Funakoshi et al teach that anti-CD40 antibodies, which exert stimulatory responses on B-cell proliferation (page 2787, first column, under the heading "Antibodies") resulted in the inhibition of proliferation of lymphoma cells lines, and that cross linking of the antibody resulted in a greater growth inhibition (page 2788, second column, under the heading "Effects of anti-CD40 on human B-cell lymphoma proliferation in vitro"). Funakoshi et al teach that soluble CD40 ligand also inhibited lymphoma

growth in vitro (pp.2788-2791, under the heading "Effects of soluble CD40 ligand on human B-cell lymphoma"). Funakoshi et al teach that the anti-CD40 antibodies administered to mice significantly inhibited the growth of transplanted human B-cell lymphomas (page 2791, first column, last full sentence). Funakoshi et al do not teach the administration of both the anti-CD40 antibody and the CD40 ligand. Funakoshi et al do not teach the humanized S2C6 antibody.

Unkun et al teach that chronic lymphocytic leukemias and non-Hodgkin's lymphomas express the CD40 antigen (abstract).

Bjorck et al teach that S2C6 synergizes with gp39 in the triggering of proliferation through the activation of the CD40 receptor. Table 2 of Bjorck et al teaches the synergism of gp39 and S2C6 in the proliferation of B cells: entries five and six indicate the uptake of tritiated thymidine in B-cells resulting from contact with S2C6 at two different concentration, entries 9 and 10 indicate the uptake of tritiated thymidine in B-cells resulting from contact with gp39 at two different concentrations, entries 19 and 20 indicate the uptake of tritiated thymidine resulting from contact with both S2C6 and gp39. It is clear from this data that the resulting proliferation induced by the combination of S2C6 and gp39 is far in excess from that expected from an additive effect of S2C6 and gp39.

DeBoar teaches that anti-CD40 antibodies known in the art prior to the disclosure of DeBoar have a stimulatory effect on human B cells (column 2, lines 45-46 and 62-64). DeBoar teaches that the prior art anti-CD40 antibodies mimic the effect of T-helper cells and thus can replace the T cell helper signal (column 2, lines 51-59). DeBoar teaches "new" antibodies such as 5D12, 3C6 and 3A8 which differ from the prior art anti-CD40 antibodies in that the new antibodies inhibit the B-cell stimulatory response (column 2, lines 62-67). DeBoar teaches S2C6 as an "old" antibody, (in contrast to the "new" antibodies) which stimulates B-cell proliferation (column 17, lines 57-62, and the description for Figures 5 and 6). DeBoar teaches that the "new" antibodies can inhibit stimulatory signals elicited by the "triggering "of CD40 with another antibody (column 18, lines 36-40). Boar teaches that the administration of humanized versions of the "new" antibodies would be efficacious in the treatment of antibody-mediated autoimmune diseases (column 3, lines 52-65 and column 4, lines 14-19).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat lymphoma by the administration of trigger the humanized or chimerized S2C6 antibody and gp39. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Funakoshi et al on the induction of cell death in malignant B cells by the administration of a CD40 ligand or a anti-CD40 antibody which normal results in activation of proliferation on normal B-cells; the teachings of De Boar on the activation of proliferation induced by S2C6 and the teachings of Bjorck et on the synergism of gp39 and S2C65 in the proliferation of B cells.

Applicant has previously argued against the teachings of Bjorck et al stating that they taught away from the instant invention because of the results of the ELISA assay presented in Table 4, wherein it is indicated that S2C6 inhibits the binding of gp39 by 57.9%. This has been considered but not found persuasive. Table 2 of Bjorck et al teaches the synergism of gp39 and S2C6 in the proliferation of B cells: entries five and six indicate the uptake of tritiated thymidine in B-cells resulting from contact with S2C6 at two different concentration, entries 9 and 10 indicate the uptake of tritiated thymidine in B-cells resulting from contact with gp39 at two different concentrations, entries 19 and 20 indicate the uptake of tritiated thymidine resulting from contact with both S2C6 and gp39. It is clear from this data that the resulting proliferation induced by the combination of S2C6 and gp39 is far in excess from that expected from an additive effect of S2C6 and gp39. Further, the results in Table 4 which indicate that S2C6 inhibits the biding of gp39 in the ELISA assay are not germane to the instant case because said data is for the binding of S2C6 and gp39 to the CD40-Ig fusion protein which was immobilized on the surface of the 96-well plate (page 431, second column, lines 3-12, under the heading "Epitope analysis"). Given that the results of the activation of cellular proliferation presented in Table 2 showed synergistic effects with the addition of S2C6 and gp39, one of skill in the art would reasonably conclude that ELISA data on the competition with binding to a CD40-Ig coated solid support does not accurately mimic CD40 receptor on a cell surface.

16. Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 58-66, 68, 75-77, 79, 80, 83-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francisco et al (The Journal of Biological Chemistry, 1997, Vol. 272, pp. 24165-24169, cited in a previous Office action) in view of Paulie

et al (Cancer Immunology, Immunotherapy, 1985, Vol. 20, pp. 23-28, cited in a previous Office action) and DeBoar (U.S. 5,874,082) and Schlom (Molecular Foundations of Oncology, S. Broader, Ed., 1991, pp. 95-134, cited in a previous Office action). Claim 58 embodies a method for the treatment of cancer comprising administering a molecule comprising SEQ ID NO:8, 9 and 10, which molecule binds CD40 and is a fusion protein. Claim 66 embodies the method of claim 58 wherein the molecule comprises the amino acid sequence of bryodin fused to SEQ ID NO:7 and SEQ ID NO:2. Claims 38, 39 and 40 embody the methods of claims 26, 27 and 37, respectively, wherein the molecule is conjugated to a chemotherapeutic agent. Claims 79 embodies the methods of claims 61 or 62 wherein the molecule is conjugated to a chemotherapeutic agent. Claim 80 embodies the method of claim 75 wherein the antibody is conjugated to a chemotherapeutic agent. Claims 97-99 embody the methods of claims 26, 37, 58, 59, 63, 64, 87 and 91 wherein the cancer is a carcinoma. Claims 109-111 embody the methods of claims 97, 98 and 99, wherein the carcinoma is lung carcinoma or bladder carcinoma.

Francisco et al teaches that the toxin bryodin fused to the sFv fragment of the G28.5 antibody which binds to CD40 is cytotoxic to a non-Hodgkin's lymphoma cell line, a multiple myeloma cell line , a b-cell leukemia and a Hodgkin's disease cell line. Francisco et al teach that all these cell lines express CD40. Francisco et al teach that because the single chain immunotoxin comprising bryodin was cytotoxic without the addition of a translocation domain, this is indicative that bryodin itself possesses said translocation domain (page 24169, first column, lines 3-15). Because bryodin kills cancer cells, it is concluded that bryodin is a chemotherapeutic agent. Francisco et al also teach that G28.5 fused to Pseudomonas endotoxin was toxic to lung, breast, colon and ovarian carcinoma cell in vitro (page 24168, Table I)

Paulie et al teach that the S2C6 antigen is found on bladder cancer cells and on B lymphocytes (abstract lines 15-19). Paulie et al teach that the S2C6 epitope is part of the CD40 receptor (abstract, lines 1-3).

deBoer teaches how to make humanized anti-CD40 antibodies. deBoer does not specifically make a humanized anti-CD40 S2C6 antibody.

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of murine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the

HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the murine antibodies (pages 97-98, bridging paragraph). Schlom teaches that single chained antibodies and Fab antibody fragments have increased ability to penetrate through tumor masses in contrast to whole antibodies (page 119, second column first paragraph under the heading "Single Chain antigen Binding Proteins").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat B cell malignancies by the administration of a humanized S2C6 antibody conjugated or fused to bryodin, and to treat bladder, lung and ovarian carcinomas by the administration of a humanized S2C6 antibody fused to Pseudomonas endotoxin, wherein the S2C6 antibody was a tetravalent full antibody or a single chain Fv fragment. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Francisco et al on the cytotoxicity of bryodin fused to anti-CD40 antibodies on B cell malignancies and the cytotoxicity of pseudomonas endotoxin fused to an anti-CD40 antibody on carcinoma cells, and the teachings of Paulie et al on the presence of the S2C6 epitope on bladder carcinomas. One of skill in the art would reasonable conclude that cancer cells which overexpress CD40 will be bound by the molecules, proteins and antibodies derived from the S2C6 antibody, and that the translocation domain of bryodin will allow for internalization of bryodin into the cytoplasm of the cancer cell.

Applicant argues that Francisco taught against the instant invention because Francisco taught that the bryodin fusions with the G28.5 antibodies were not toxic to carcinoma cells. This has been considered but not found persuasive because claim 66 is the only claim specifically embodying bryodin. Thus, it would be obvious to one of skill in the art that bryodin fusion proteins targeted to the CD40 antigen would be toxic on hematological malignancies, whereas pseudomonas exotoxin fusion proteins targeted to the CD40 antigen would be toxic to lung, bladder or ovarian carcinoma cells.

17. Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 83-93, 97-99 and 109-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melief et al (U.S. Application 2003/0022860, priority to May 23, 1998) and de Boer (U.S. 5,874,082) as applied to claims 26,

27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77 and 83-93 above, and further in view of Slingluff et al (WO 98/33810). The specific embodiments of claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77 and 83-93 are set forth above. Claims 97-99 embody the methods of claims 26, 27, 59, 63, 64, 87 and 91, wherein the cancer is a carcinoma. Claims 109-111 embody the methods of clams 97-99 wherein the carcinoma is a lung carcinoma or a bladder carcinoma. Claims 112-114 embody the methods of claims 109-11 wherein the lung carcinoma is a small cell or non-small cell lung carcinoma. The combination of Melief et al and Bjorck et al render obvious a method of treating cancer comprising the administration of a humanized or chimeric S2C6 antibody in a vaccine comprising a CTL-activating tumor peptide for the reasons set forth above. The combination does not specifically address the treatment of lung cancer or bladder cancer.

Slingluff et al teach a method of treating cancer comprising the administration of CTL-activating tumor peptides (page 2, lines 2-5, page 6, lines 7-12, 14-18). Slingluff et al specifically identify peptide epitopes for human tumor-specific CTL derived from proteins such as MAGE 1, MAGE-3, BAGE and GAGE-1 and 2 which are expressed in bladder carcinoma and non-small cell lung carcinoma (page 27, Table A and page 28, lines 1-9, under the table). Slingluff et al teach that the CTL epitopes , when used in oligopeptide form to reconstituted epitopes for CTL, achieve lysis of target cells (page 14, line 33 to page 15, line 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the MAGE-1, 3, BAGE or GAGE-1, 2 tumor-specific CTL peptides taught by Slingluff et al to be present in the method of treating generic cancer as rendered obvious by the combination of Melief et al and Bjorck et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Slingluff et al on the tumor-specific CTL-epitopes which are present in bladder and non-small cell lung carcinoma.

18. Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 58-66, 68, 75-77, 79, 80, 83-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francisco et al (The Journal of Biological Chemistry, 1997, Vol. 272, pp. 24165-24169) in view of Paulie et al (Cancer Immunology, Immunotherapy, 1985, Vol. 20, pp. 23-28,) and DeBoar (U.S. 5,874,082) and Schlom (Molecular

Foundations of Oncology, S. Broader, Ed., 1991, pp. 95-134) as applied to claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 58-66, 68, 75-77, 79, 80, 83-96 and 100-108 above, and further in view of the abstract of Kawaguchi et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A2319).

Claims 112-114 embody the methods of claims 109-111 wherein the lung carcinoma is small cell or non-small cell. The combination of Francisco et al and Paulie et al and deBoar and Schlom render obvious the claimed methods wherein the cancer is a hematological malignancy or a bladder carcinoma. It is noted that Francisco et al teach that the G28.5 pseudomonas endotoxin fusion protein is cytotoxic to the L2987 lung cancer cell line. The combination does not specifically teach the treatment of small cell or non-small cell lung cancer

The abstract of Kawaguchi et al teaches that non-small cell lung cancers were found to express CD40 on the cell surface.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer a humanized S2C6 antibody, or a single chain or Fab fragment derived from the S2C6 antibody, wherein said antibodies and fragments were conjugated to pseudomonas endotoxin for the treatment of non-small cell lung carcinoma. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Kawaguchi et al which identified the CD40 antigen as expressed on the surface of non-small cell lung carcinomas.

19. Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 83-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Funakoshi et al (Blood, 1994, Vol. 83, pp. 2787-2794) and Bjorck et al (Immunology, 1994, Vol. 83, pp. 430-437) and deBoar (U.S. 5,874,082) and by Unkun et al (Blood, 1990, Vol. 76, pp. 2449-2456) as applied to claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 83-96 and 100-108 above, and further in view of the abstract of Kawaguchi et al et al (Proc Annu Meet Am Assoc Cancer Res, 1997, Vol. 38, page A2319). The specific embodiments of the claims are set froth above.

The combination of Funakoshi et al and Bjorck et al and deBoar and Unkun et al render obvious a method of treating hematological malignancies by the administration of the gp39

ligand and a humanized S2C6 antibody for the reason set forth above. The combination of references do not teach a method of treating non-small cell lung carcinoma.

The abstract of Kawaguchi et al teaches that a soluble CD40 ligand trimer was able to suppress the proliferation of eight different tumors derived from lung tumor biopsy tissue. The abstract of Kawaguchi et al suggest that CD40 on human non-small cell lung tumors transduces signals that can affect the biological activity of the tumor.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat non-small cell lung cancer by the method rendered obvious by the combination of Funakoshi et al and Bjorck et al and deBoar and Unkun et al: administration of the gp39 ligand and a humanized S2C6 antibody.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Kawaguchi et al on the suppressive effect on non-small cell lung tumors induced by contact of said tumors with a soluble CD40 ligand trimer. One of skill in the art would conclude that triggering of the CD40 receptor by binding with the ligand induced a suppressive effect on the lung tumors and that the same mechanism whereby hematological malignancies were suppressed by the triggering of the CD40 receptor was operative in the non-small cell lung tumors. Thus, it would be obvious that the administration of the humanized S2C6 antibody in combination with the gp39 ligand would result in a synergistic triggering of the CD40 receptor and the inhibitory signal induced by the receptor triggering would therefore be greater.

20. All other rejections and objections as stated in Paper No. 7 are withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.

Art Unit 1642

10/09/03